Given the epidemiology of human leishmaniasis and AIDS in Brazil, numerous cases of *Leishmania*/HIV co-infection might be expected. Relatively few Brazilian cases have been reported, however, even from regions where the overall incidences of HIV and *Leishmania* infection are both relatively high. Many cases of co-infection probably go undetected because of a lack of awareness among clinicians or limited access to appropriate diagnostic methods.

In contrast to the situation in Europe, intravenous-drug users do not predominate among those exposed to HIV infection in Brazil. The success of the Brazilian programme for the free and universal distribution of antiretroviral drugs has decreased the prevalences of the commoner opportunistic infections among HIV-positives and increased the longevity of AIDS cases. Recent changes in the epidemiological patterns of HIV and *Leishmania* infections are likely to lead to a greater degree of overlap and a greater risk of co-infection and they justify increased alertness. This review of the co-infection in Brazil addresses three main topics: the current situation, in terms of the epidemiology of AIDS and *Leishmania* infection; the related epidemiological trends and their likely impact on the co-infection; and the co-infection cases reported in Brazil by June 2003.

**AIDS IN BRAZIL**

The first known Brazilian case of AIDS was reported in São Paulo, in 1980. HIV was probably introduced into the large metropolitan areas of southern–central Brazil in the late 1970s, spreading to other ‘macro-regions’ in the first half of the 1980s. According to the Brazilian Ministry of Health’s AIDS Programme, 257,780 cases of AIDS were reported in Brazil between 1980 and 2002. The results of seroprevalence surveys in 2000 indicated that 6.5 of every 1000 individuals aged 15–49 years were then HIV-positive ([www.aids.gov.br](http://www.aids.gov.br)). The annual incidence of HIV infection has been slowly falling in recent years, from 15.9 cases/100,000 in 1998 to 12.3/100,000 in 2001 ([www.aids.gov.br](http://www.aids.gov.br)).

Over the last decade, however, the epidemiological profile of the HIV/AIDS epidemic in Brazil has shown three major changes:

1. **Increasing Prevalence of AIDS among Women and Heterosexual Men**

Prior to 1990, homosexuals formed the main group affected by HIV/AIDS. From 1987 onwards, however, the percentage of HIV-positives who were heterosexual gradually increased, and heterosexual cases have outnumbered the homosexual and bisexual since 1994 (Fig. 1).

   The overall male:female ratio for AIDS cases in Brazil has also shown important changes over time, falling from 23:1 in 1984 to 3:1 in 1996 and just 2:1 since 2000. In recent years, an AIDS case aged 13–19 years is more likely to have been female than male, with male:female ratios of 0.9:1, 0.9:1, 0.8:1 and 0.6:1 in 1998, 1999, 2000 and 2001, respectively (Fig. 2; [www.aids.gov.br](http://www.aids.gov.br)).
FIG. 1. The annual numbers of Brazilian AIDS cases assigned to the main exposure-groups of homosexual (■), bisexual (●), heterosexual (▼), intravenous-drug user (▲), haemophiliac (▲) and patient receiving blood transfusions (■), for the period 1982–2002.

FIG. 2. The annual numbers of male (■) and female (□) AIDS cases recorded in Brazil, for the period 1982–2002.
2. Increasing Incidence among the Poorly Educated
In 1984, 84% of diagnosed cases of AIDS had been educated to high-school or college level. By 1994, however, 65% of such cases were illiterate or had been educated only to primary school level. In 2000, 58.9% of the reported cases had <8 years of formal education, compared with 33.4% in the 1980s.

3. A marked reduction in AIDS-related mortality
In 1991, Zidovudine (AZT) became available for distribution through the Brazilian public-health system, and HIV carriers and AIDS patients have had free and universal access to all antiretroviral drugs, including protease inhibitors, since 1996. According to the Ministry of Health, coverage of eligible patients was close to 100% in 2003, with approximately 125,000 patients receiving antiretroviral medication. Annual AIDS-attributable mortality was almost halved between 1995 and 1999, falling from 12.2 deaths/100,000 to 6.3 deaths/100,000 (www.aids.gov.br). In large urban centres such as São Paulo and Rio de Janeiro, which account for >31% of the known AIDS cases in the country, the decrease in mortality has been even more marked (approximately 70% between 1995 and August 2000). In addition, among patients with HIV/AIDS, there have been marked decreases in the prevalences of the main opportunistic conditions associated with severe immunodeficiency — a 60% decrease in cryptococcosis, a 54% decrease in cytomegalovirus and a 38% decrease in Kaposi’s sarcoma (www.aids.gov.br).

HUMAN LEISHMANIASIS IN BRAZIL
The reported prevalence of human leishmaniasis, a serious health problem in Brazil, has increased considerably in recent years (Fig. 3). The most important Leishmania spp. in the country are L. (Leishmania) chagasi, causing visceral leishmaniasis (VL), and L. (Viannia) braziliensis, L. (V.) guyanensis and L. (L.) amazonensis, which each cause cutaneous leishmaniasis (CL). Although both VL and CL are widely dispersed, there tends to be a predominance of one form in each region.

Between 1980 and 1991, the Ministry of Health recorded annual means of 22,000 new cases of cutaneous, mucocutaneous or mucosal leishmaniasis (together labelled tegumentary leishmaniasis or TL) and 1500 new cases of VL. In 2002, however, 33,720 cases of TL and 4880 of VL were reported (www.funasa.gov.br). Between 1982 and 2002, the annual incidence of leishmaniasis varied from 0.96 to 2.66 cases/100,000. Like the antiretroviral drugs, the antimonal compounds used in the treatment for leishmaniasis are financed and distributed by the Brazilian government.

Growth of the Brazilian population, accelerating urbanization, man-made environmental changes and massive rural–urban migration have contributed to the spread of leishmaniasis into new areas. These changes have also resulted in modifications to the epidemiological pattern of leishmanial infection, bringing large numbers of individuals into already densely populated urban areas and into contact with the causative parasites. Many urban outbreaks of VL have been observed, in different regions of the country, over the last decade (Passos et al., 1993; Jeronimo et al., 1994; Vasconcelos et al., 1998; Luz et al., 2001).

Leishmania/HIV CO-INFECTION IN BRAZIL
By June 2003, almost 100 cases of Leishmania/ HIV co-infection had been reported, either in the formal scientific literature (Coura et al., 1987; Rodrigues et al., 1987; Calich et al., 1991; Cunha et al., 1991; Moreira et al.,
FIG. 3. The annual numbers of cases of cutaneous and visceral leishmaniasis reported in Brazil between 1982 and 2002. The data shown for 2002 relate only to the first half of the year.

1991; Da-Cruz et al., 1992, 1999; Machado et al., 1992; Borges-Filho et al., 1996; Machado et al., 1996; Morimoto et al., 1996; Sasaki et al., 1997; De Souza e Souza et al., 1998; Matos et al., 1998; Rabello et al., 1998; Rosatelli et al., 1998; Borges et al., 1999; Chehter et al., 1999; Cimmerman and Gomes, 1999; Sampaio et al., 1999, 2000, 2002; Silva et al., 1999; Takeda et al., 1999; Amato et al., 2000; Hueb et al., 1998, 2000; Pereira et al., 2000; Ferreira et al., 2001; Bittencourt et al., 2002; Orsini et al., 2002; Silva et al., 2002; Ribeiro et al., 2003) or in the informal proceedings and abstracts of scientific meetings held in 1989 (E. L. Nicodemo), 1991 (A. F. Araújo), 1992 (J. Carnaubá), 1993 (G. M. Borges-Filho, and A. Q. Souza), 1994 (K. Osaki, A. Porro, and G. M. Viana), 1995 (M. C. de O. Gomes, V. Leal, and E. Santos), 1996
In 2002, as an activity of the World Health Organization’s (WHO’s) global network for the surveillance of *Leishmania/HIV*

**FIG. 4.** The biennial (■) and cumulative (□) numbers of *Leishmania*/HIV co-infection cases in Brazil and the corresponding annual numbers of AIDS cases (■), for the period 1982–2002.
co-infection, all of those who had reported a Brazilian case of co-infection (formally in the literature or informally, at a conference or as a personal communication) were contacted and asked to complete the WHO’s standardized form for reporting the co-infection. (The results of initial informal searches had indicated that a considerable number of co-infection cases had never been notified or reported.) Ninety-one cases were recorded on these forms, the trend in the annual incidence of the co-infection cases matching that of AIDS (Fig. 4).

VL accounted for 37% of the reported cases and TL for the other 63%, most of the TL cases being muco–cutaneous or mucosal (43% of all cases) rather than cutaneous (20% of all cases; Fig. 5). The age of the cases ranged from 1–62 years, with a mean of 37 years (Fig. 6), and all but seven (91.9%) were male. The age-specific distribution of the co-infection reflects that of HIV infection in Brazil.

When the Brazilian co-infection cases reported in 2002 were separated according to exposure-group (where known), most of the patients were not found to be intravenous-drug users (IVDU), although IVDU form the main risk group in Europe (Desjeux and Alvar, 2003). Again, the exposure-group data for the co-infection reflect those for HIV/AIDS in Brazil (Fig. 7).

Leishmaniasis was diagnosed before (18%), after (41%) or at the same time (46%) as the HIV infection. The corresponding percentages for TL (mucosal, cutaneous or muco–cutaneous forms) were 18%, 46% and 36%, respectively, whereas those for VL were 14%, 57% and 29%, respectively (Fig. 8). Diagnosis of VL was based primarily on the detection of parasites in bone marrow whereas TL was generally confirmed by the direct examination of smears of skin or mucosal biopsies (Fig. 9).

The Leishmania parasites were only identified, to at least subgeneric level, in 12 of the co-infection cases (eight of cutaneous, three of muco–cutaneous and one of visceral leishmaniasis). Three cases were found to be infected with Leishmania (Viannia) spp.,
seven with *L. (V.) braziliensis* and one with *L. (V.) guyanensis* (Coura et al., 1987; Da-Cruz et al., 1992; Machado et al., 1996; Matos et al., 1998; M. C. de. O. Gomes, unpubl. obs.). The VL case was caused by *L. (L.) chagasi* (Orsini et al., 2002).

**ESTABLISHMENT OF A SURVEILLANCE NETWORK**

Recent data indicate that the HIV epidemic is still spreading in Brazil, reaching small cities, increasingly affecting women, and extending to populations with relatively low levels of education. At the same time as HIV infection is becoming less concentrated in urban areas, human leishmaniasis is becoming less rural (Luz et al., 2001). In Brazil, the traditionally marginalized populations — who are already continuously exposed to the burden of endemic diseases, unemployment, ignorance, hunger and lack of healthcare — live in peri-urban areas, where the geographical distributions of HIV and leishmaniasis increasingly overlap. It is these populations who are at greatest risk of *Leishmania*/HIV co-infection.

The Brazilian STD/AIDS Programme has succeeded in setting up a network to monitor and control HIV infection throughout the country. Between 1994 and 1998, a budget of U.S.$250 million financed the establishment of testing/counselling centres, care units staffed with healthcare providers, teams of instructors and supervisors of community healthworkers, a family-health programme, hospitals accredited for HIV/AIDS care, dispensing units for AIDS drugs, and laboratories that could determine viral loads and perform counts of CD4+ lymphocytes. There is also a National Sentinel Network for HIV surveillance, local trends in HIV prevalence being monitored from centres in all 26 federal states. In contrast to the well organized and supported HIV/AIDS-control interventions, the control of leishmaniasis in Brazil depends mainly on the relatively weak structure of the basic public-health system. The levels of control and of the epidemiological assessment of leishmaniasis vary greatly with the local infrastructure and local levels of political commitment and community involvement. In many remote cities, community health-workers expect little help in the diagnosis, treatment or prevention of leishmaniasis.
FIG. 8. The first infection diagnosed in each case of *Leishmania*/HIV co-infection reported in Brazil by June 2003, shown for all cases and separately for those with visceral or tegumentary leishmaniasis.

The establishment of a national surveillance network for *Leishmania*/HIV co-infection is clearly a priority. It would seem sensible to add surveillance and control of the co-infection to the pre-existing network for the monitoring and control of HIV/AIDS. This initiative has been discussed and is currently being organized by the Brazilian STD/AIDS Programme, the scientific community and the Leishmaniasis Division of the Brazilian Ministry of Health. The aims of the proposed co-infection network have been set, tentatively, to include:

- (1) the mapping of the geographical distribution of the co-infection;
- (2) the evaluation of the epidemiological, clinical, immunological and therapeutic characteristics of each identified case;
- (3) increasing the availability of diagnostic tests for leishmaniasis (and ensuring that they are used correctly);
- (4) the setting up reference laboratories for the isolation and characterization of the parasites;
- (5) improvement in the dissemination of relevant information;
FIG. 9. The numbers of HIV-positive individuals found, as the result of various laboratory tests, to have concurrent, visceral or tegumentary leishmaniasis in Brazil by June 2003.

(6) improving training and providing appropriate guidelines for the health system;
(7) broadening the participation of ‘grass-root’ and non-governmental organizations; and
(8) the planning and evaluation of control interventions and follow-up activities.

As a first step to fulfilling aims 3 and 4, an advisory group of the Brazilian STD/AIDS Programme has recently prepared a set of guidelines on the co-infection (Anon., 2003). These include a list of clinical features that might be indicative of the co-infection and that should, in consequence, be carefully investigated. They also outline the conditions under which patients with leishmaniasis should be offered HIV tests (Tables 1 and 2) and consenting patients with HIV/AIDS should be tested for Leishmania infection (Table 3). As the main objective of these guidelines is simply to encourage clinicians to consider the possibility of Leishmania/HIV co-infection in their differential diagnoses, they are wide-ranging and not definitive.

Hopefully, these initial steps in the establishment of a national surveillance network will improve the detection, control and prevention of Leishmania/HIV co-infection in Brazil.

ACKNOWLEDGEMENT. The authors thank Dr D. Greco for critically reviewing the original manuscript.
### TABLE 1. Clinical conditions under which patients with tegumentary leishmaniasis should be offered HIV tests

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Development of any clinical form of leishmaniasis more than a year after the patient was in an area where human infection with <em>Leishmania</em> occurs</td>
</tr>
<tr>
<td>● Disseminated clinical form with or without mucosal involvement</td>
</tr>
<tr>
<td>● Mucosal clinical form with extra-nasal lesions</td>
</tr>
<tr>
<td>● Cutaneous or mucosal clinical forms with parasites observed in the viscera</td>
</tr>
<tr>
<td>● Diffuse clinical form</td>
</tr>
<tr>
<td>● Any clinical form in a patient giving a negative result in a (Montenegro) skin test</td>
</tr>
<tr>
<td>● Presence of amastigotes in a smear of a mucosal lesion</td>
</tr>
<tr>
<td>● Isolation of <em>Leishmania</em> (<em>L.</em>) <em>chagasi</em> (or other normally viscerotropic <em>Leishmania</em> sp.) from skin or mucosal lesions</td>
</tr>
<tr>
<td>● Therapeutic failure with a pentavalent antimonial drug*</td>
</tr>
<tr>
<td>● Late relapse (&gt;6 months after clinical recovery)</td>
</tr>
<tr>
<td>● Cutaneous lesions appearing after active mucosal lesion</td>
</tr>
</tbody>
</table>

*Absence of clinical cure after two attempts at treatment with meglumine antimoniate (10–20 mg Sb/V/kg.day for 20–30 days), with a 3-month follow-up after each period of treatment.

### TABLE 2. Clinical conditions under which patients with visceral leishmaniasis (VL) should be offered HIV tests

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Development of any clinical form of leishmaniasis more than a year after the patient was in an area where human infection with <em>Leishmania</em> occurs</td>
</tr>
<tr>
<td>● Patient an intravenous-drug user</td>
</tr>
<tr>
<td>● Absence of anti-leishmanial antibodies in a patient with the typical symptoms of VL</td>
</tr>
<tr>
<td>● Presence of circulating amastigotes</td>
</tr>
<tr>
<td>● Involvement of systems/organs rarely affected in VL*</td>
</tr>
<tr>
<td>● Therapeutical failure after treatment with pentavalent antimonial†</td>
</tr>
<tr>
<td>● Late relapse‡</td>
</tr>
<tr>
<td>● Development of other infections indicative of immunodeficiency, during or after treatment§</td>
</tr>
<tr>
<td>● Isolation of a normally dermotropic species of <em>Leishmania</em></td>
</tr>
</tbody>
</table>

*Such as the respiratory tract, digestive tract or skin.
†Absence of clinical cure after two attempts at treatment with meglumine antimoniate (10–20 mg Sb/V/kg.day for 30 days), with a 3-month follow-up after each period of treatment.
‡After at least 12 months of clinical recovery.
§Such as herpes zoster or tuberculosis.

### TABLE 3. Clinical conditions under which HIV/AIDS cases should be checked for tegumentary or visceral leishmaniasis

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Any cutaneous or mucosal lesion lasting more than 2 weeks in patients who have been exposed to <em>Leishmania</em> transmission in their lifetime*</td>
</tr>
<tr>
<td>● Fever associated with hepatomegaly, splenomegaly or cytopenia in a patient who has been to an area of <em>Leishmania</em> transmission and/or used intravenous drugs</td>
</tr>
</tbody>
</table>

*Areas of transmission are considered to be those municipalities where at least one case of human leishmaniasis has been reported.
REFERENCES


